A Novel Engineered Niche to Explore the Vasculogenic Potential of Embryonic Stem Cells

Grant Award Details

A Novel Engineered Niche to Explore the Vasculogenic Potential of Embryonic Stem Cells

Grant Type: New Faculty I

Grant Number: RN1-00566

Investigator:

Name:	Andrew Putnam
Institution:	University of California, Irvine
Type:	PI

Disease Focus: Heart Disease

Human Stem Cell Use: Adult Stem Cell, Embryonic Stem Cell

Award Value: $395,764

Status: Closed

Grant Application Details

Application Title: A Novel Engineered Niche to Explore the Vasculogenic Potential of Embryonic Stem Cells

Public Abstract: Cardiovascular diseases account for an estimated $330 billion in health care costs each year, afflict 61.8 million Americans, and will account for more than 1.5 million deaths in the U.S. this year alone. A number of these diseases are characterized by either insufficient blood vessel growth or damage to the existing vessels, resulting in inadequate nutrient and oxygen delivery to the tissues. The most common clinical example of this is a heart attack, or myocardial infarction, typically caused by blockage of a coronary artery. The resulting ischemia (reduced blood flow) induces irreversible damage to the heart, leaving behind a non-functional scar tissue. Efforts to restore blood flow to ischemic tissues have largely focused on the delivery of protein growth factors (called pro-angiogenic molecules) that stimulate new capillary growth. An alternative approach is to deliver an appropriate cell type that can either accelerate the recruitment of host vessels or can differentiate into a functional vasculature directly. While adult stem cells have shown promising potential with respect to the former, the potential of embryonic stem cells (ESCs) with respect to either of these two possibilities remains unclear. Therefore, this proposal seeks to: 1.) Utilize a novel, highly tunable, 3D engineered niche to investigate how changes in multiple instructive signals coordinately govern the differentiation of ESCs into capillary vessels; 2.) Exploit knowledge gained from basic studies using this model system to generate a purified population of ESC-derived endothelial progenitor cells (EPCs) and test their potential to repair ischemia in vivo. Specifically, in Aim 1, we propose to further develop and characterize our artificial engineered niche for fundamental studies on ESC fate decisions. Aim 2 will use this system to test two competing hypotheses, namely that: 1.) ESCs can facilitate capillary morphogenesis in an indirect manner, in much the same way as adult stem cells; or 2.) ESCs can be directed down an endothelial-specific lineage by manipulating one or more instructive signals. Finally, Aim 3 will utilize our engineered niche to generate a purified population of ESC-derived EPCs and then test their ability to enhance perfusion in an animal model. Successful completion of these proposed aims may transform the clinical use of stem cells for cardiovascular disease and other ischemic pathologies by enabling identification of those factors and conditions which promote vessel formation. The versatile artificial engineered niche developed here will also yield a new tool that could enormously benefit efforts to screen the combinatorial effects of promising therapeutic compounds. Completion of the planned studies will greatly facilitate the PI's long-term goal of developing "instructive" biomaterials and strategies to direct tissue repair.

Statement of Benefit to California:	Human embryonic stem cells (hESCs) are pluripotent stem cells that can theoretically give rise to every cell type in the human body. Their potential use for the treatment of human diseases has been heralded with great fanfare and even some controversy. However, their therapeutic potential has yet to be realized due to an incomplete fundamental understanding of the factors that govern their differentiation. This proposal describes studies intended to assess the ability of hESCs to develop into blood vessels; in particular, capillary networks that are responsible for the delivery of oxygen and essential nutrients to all tissues in the human body. This focus is motivated by the fact that cardiovascular disease accounts for an estimated $330 billion in health care costs each year, afflicts 61.8 million Americans, and will account for more than 1.5 million deaths in the United States this year alone. It is the number one killer in this country and in California. Since many cardiovascular diseases are characterized by either insufficient blood vessel growth or damage to the existing vessels, a therapy based on hESCs could have enormous benefit to the citizens of California, the United States, and the rest of the world. Therefore, this proposal has two primary goals. First, we seek to develop a novel technology to systematically investigate the influence of multiple instructive signals on the ability of hESCs to differentiate into capillary vessels. Second, we propose to exploit knowledge gained from the basic studies using this technology to generate a purified population of hESCs and test their potential to repair ischemia (lack of blood flow) in an animal model. Successfully achieving these goals will benefit the citizens of California in three significant ways. First, our efforts may help to transform the clinical use of stem cells, not only for cardiovascular disease but other diseases as well, by enabling identification of those factors and conditions which promote hESC differentiation. Second, the versatile technology developed here will yield a powerful new tool that could enormously benefit California's biotechnology companies in their efforts to screen the combinatorial effects of promising therapeutic compounds. Third, we expect the proposed studies to directly benefit 8-10 researchers in training and indirectly trickle down to hundreds of undergraduate students [REDACTED] enrolled in courses taught by the PI. This final benefit may perhaps have the most significant long-term economic impact by training and inspiring future leaders to pursue research and development positions in California.

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